REMARKS

Claims 1, 5-11, and 13-16 are pending in the instant application. Claim 1, 5-11, and 13-16 stand objected to because of an informality in claim 1. Claims 1, 5-11, and 13-16 stand rejected under 35 U.S.C. §103(a) as being unpatentable over United States Patent No. 6,574,495 to Golman et al. or United States Patent No. 6,278,893 to Ardenkjaer-Larsen et al. in view of either United States Patent No. 5,245,282 to Mugler et al. or United States Patent No. 6,310,478 to Held. The application has been amended. Claim 1 has been amended by making step iv) mandatory and amendments have been included to more particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully submit that none of the amendments constitute new matter in contravention of 35 U.S.C. §132. Reconsideration is respectfully requested.

Claim 1, 5-11, 13-16 are objected to because these claims are directed to a method of imaging while step iv is optional. Applicants respectfully submit that this objection stands obviated in view of the amendment to claim 1 deleting the term "optional" in step iv). Reconsideration and withdrawal of the objection is respectfully requested.

Claims 1, 5-11, 13-16 stand rejected under 35 U.S.C. §103(a) as being unpatentable over United States Patent No. 6,574,495 to Golman et al. or United States Patent No. 6,278,893 to Ardenkjaer-Larsen et al. in view of either United States Patent No. 5,245,282 to Mugler et al. or United States Patent No. 6,310,478 to Held. This rejection is respectfully traversed.

Claim 1 has been amended by more particularly pointing out in step iii) that the MR imaging agent exhibits variations in relaxation time T2 as a result of physiological changes or as a result of metabolism in said sample.

As stated in Applicants response of October 16, 2009, the technical problem solved by using a FISP or PSIF pulse sequence with a flip angle of 45 to 90 degrees for a hyperpolarised imaging agent in liquid phase is to avoid a reduced signal due to increased T_2 relaxation rate of the imaging agent. Such an increased T_2 relaxation is caused by physiological changes (e.g. pH or temperature) or short half life of the imaging agent due to metabolism (see page 14, 3rd paragraph of the present application) – the latter being most important since the imaging agent of the present invention is a compound of interest in metabolic studies, i.e. a compound that is metabolised. Claim 1 has been amended to more clearly recite this.

Golman et al. or Ardenkjaer-Larsen et al. disclose methods of MR imaging using hyperpolarised MR agents in liquid phase. Both Golman et al. and Ardenkjaer-Larsen et al. fail to disclose the features of the method of the invention or using both a FISP or PSIF pulse sequence with a flip angle of 45 to 90 degrees. Further, there is no suggestion by Golman et al. or Ardenkjaer-Larsen that the MR imaging agent exhibits variations in relaxation time T2 as a result of physiological changes or as a result of e.g. metabolism or other physiological changes.

Mugler et al. and Heid disclose a FISP pulse sequence which is used in MR imaging methods. However, neither reference discloses, teaches, or suggests liquid hyperpolarised MR imaging agents. The prior art discussion about FISP and steady state imaging is exclusively related to thermally polarised liquid compounds. Moreover, the relationships that are true for thermally polarised liquid compounds are not applicable for hyperpolarised liquid compounds.

In the Office Action of May 14, 2009, it is stated that "it would have been obvious … to employ a steady-state of the complete magnetization vector producing greater image quality.". Applicants respectfully point out that this is not the case. By its very nature, the non-thermal magnetization generated by the hyperpolarization process is non-renewable; hence *there is no steady state*. Rather, the magnetization relaxes back to thermal equilibrium in an irreversible fashion. Failure to recognize this – and to thus make an attempt to optimize FISP or PSIF sequence parameters according to prior art – will inevitably lead to failure of the imaging technique. Applicants submit that the very realization that the flip angle has to be optimized in a different manner for the non-renewable magnetization is non-obvious, non-trivial, and distinguishes the present invention over prior art.

In view of the above, the statement that mere "substitution of one known type of fast pulse sequence for another would have yielded predictable results" is respectfully disputed by Applicants. There is a fundamental difference between different types of sequences. For instance, an EPI sequence flips the entire magnetization into the transverse plane. Thus, the

optimization of EPI for the case of a hyperpolarized moiety would be entirely different from the optimization of a FISP sequence.

In the absence of renewable thermal polarization, the FISP or PSIF sequence needs to be optimized by taking into account both T1 and T2. However, a further non-trivial aspect that is encountered when attempting to image hyperpolarized liquids that are pharmacologically active is the fact that e.g. changes in pH or metabolic activity cause in-vivo T2 to deviate from its value that may have been determined in a phantom experiment. In fact, Applicants have found that the T2 of pyruvate in vivo shows deviations from mono-exponential relaxation behavior. Hence, even the notion of a single well-defined T2 relaxation time may unduly trivialize the situation encountered in vivo. Optimization of the FISP imaging parameters is thus far from obvious.

In view of this Applicants respectfully submit that the use of a pulse sequence which has only been used and optimized for thermally polarised liquid MR imaging agents would not be obvious to combine with the flip angles for hyperpolarised liquid compounds. Instead the instant invention realizes that by using such a FISP or PSIF sequence with a flip angle of 45 to 90 degrees, on a hyperpolarised imaging agent in liquid phase, a reduced signal (due to increased T_2 relaxation rate of the imaging agent) could be avoided. Thus, Applicants respectfully submit that one of ordinary skill in the art would not seek to combine the cited references as suggested by the Examiner. In view of the teachings of the prior art failing to disclose, teach, or suggest the instant invention, Applicants respectfully submit that the

instant invention is patentably distinct over the cited references. Reconsideration and withdrawal of the rejection are respectfully requested.

Any questions with respect to the foregoing may be directed to Applicant's undersigned counsel at the telephone number below.

Respectfully submitted,

/Robert F. Chisholm/
Robert F. Chisholm
Reg. No. 39,939

GE Healthcare, Inc.
101 Carnegie Center
Princeton, NJ 08540
Phone (609) 514-6905
Fax (609) 514-6572

I:\IP\Response to Office Action\PN\PN0103 (11-12-09).doc